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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,203	12/31/2001	Alan Garen	OCR-679B.US	9075

22907 7590 05/14/2004

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,203	GAREN ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-53* is/are pending in the application.

4a) Of the above claim(s) *4,5,9-14,17-20,23-45 and 48-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,21-22 and 46-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/02; 1/24/03*; 7/30/03; 9/29/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-14, 17-53 are pending.

Claims 1, 6, 9, 13-14, 17, 20 have been amended; claims 15-16 have been canceled; claims 25-53 have been added in the paper filed 9/29/2003.

2. Applicant's election of Group I, claims 1-3, 6-8, 21-22 and 46-47 in the Paper filed 2/23/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 4-5, 9-14, 17-20, 23-45 and 48-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-3, 6-8, 21-22 and 46-47 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 19, lines 4, 17 and 24. Applicant is required to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01

Appropriate correction is required.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3, 6-8 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakagaki et al (Biochemistry, 30(45):10819-10824, 1991).

The claims recite a composition comprising an immunoconjugate protein having an effector domain which can induce a cytolytic immune response or cytotoxic effect against a targeted cell conjugated to a targeting domain, which is a form or mutant form of factor VII, wherein the mutant form has a serine-344→alanine substitution. "A form of factor VII" as recited in claim 47 is interpreted to be a mutant form of factor VII. Applicant is reminded that when the claim is directed to a product, the preamble is generally non-limiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02. Therefore, the intended use of the composition as a treatment of pathological conditions characterized by

neovascularization is given no patentable weight in this rejection. Claims 6-8 are product-by-process claims, thus, the method in which the immunoconjugate protein is produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claims are the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Nakagaki et al teach factor VII, wherein serine-344 is replaced with an alanine residue and the mutated factor VII is radioiodinated with ^{125}I, which is interpreted to be an effector domain. It is inherent that the radioisotope ^{125}I can induce a cytotoxic effect against a targeted cell, however, "can" is open ended, meaning that the effector domain can have that property, but also encompasses effector domains that do not necessarily induce a cytolytic immune response or cytotoxic effect against a targeted cell. Thus, Nakagaki et al anticipate the claims.

8. Claim 47 is rejected under 35 U.S.C. 102(b) as being anticipated by Contrino et al (Nature Medicine, 2(2):209-215, 1996).

Claim 47 is drawn to a composition comprising an immunoconjugate protein having an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell conjugated to a targeting domain, which

is a form of factor VII. For this rejection the phrase "a form of factor VII" is interpreted to be a factor VIIa (i.e., the activated enzymatic form of factor VII; see page 209, left column). Applicant is reminded that when the claim is directed to a product, the preamble is generally non-limiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02. Therefore, the intended use of the composition as a treatment of pathological conditions characterized by neovascularization is given no patentable weight in this rejection.

Contrino et al teach factor VIIa labeled (i.e., conjugated) with a bitoinylated Phe-Pro-Arg-chloromethyl ketone (FPR-ck-VIIa), which is interpreted to be an effector domain (see page 213, right column) and the conjugate binds tissue factor (see page 212, left column and Figure 3). For this rejection, the phrase "can induce a cytolytic immune response or cytotoxic effect against a targeted cell" is open ended, meaning that the effector domain can have that property, but also encompasses effector domains that do not necessarily induce a cytolytic immune response or cytotoxic effect against a targeted cell. Thus, Contrino et al anticipate the claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3, 6-8 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson et al (International Journal of Cancer, 73:865-870, 1997) in view of Drake et al (American Journal of Pathobiology, 134(5):1087-1097,1989) and Contrino et al (Nature Medicine, 2:209-215, 1996) and Dickinson

et al (Proc. Natl. Acad. Sci, USA, 93:14379-14384, 1996) and Berkner et al (U.S. Patent 5,861,374, 102(e) date 2/12/96).

The claims recite a composition useful in the treatment of pathological conditions characterized by neovascularization comprising an immunoconjugate protein having an effector domain which can induce a cytolytic immune response or cytotoxic effect against a targeted cell conjugated to a targeting domain, which is factor VII or mutant factor VII, which bind tissue factor and the mutant factor VII has lysine-341→alanine and serine-344→alanine substitutions and has reduced blood coagulation activity relative to wild-type factor VII. "A form of factor VII" as recited in claim 47 is interpreted to be a mutant form of factor VII. Claims 6-8 are product-by-process claims, thus, the method in which the immunoconjugate protein is produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claims are the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Olson et al teach a vascular endothelial growth factor (VEGF)-toxin conjugate that is selectively toxic to tumor vasculature (see page 866, right column). Olson et al teach that vascular endothelial growth factor receptors (VEGFR) are over-expressed in the endothelial cells of tumor vasculature and almost nondetectable in the vascular endothelium of adjoining normal tissues

and the differential expression of receptor offers a selective advantage for targeting cytotoxic toxin polypeptides (see abstract). Olson et al teach that neovascularization is characteristic of solid tumor growth (see page 865, left column). Olson et al do not specifically teach an immunoconjugate comprising factor VII or mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell, wherein the mutant factor VII has lysine-341→alanine and serine-344→alanine substitutions and the mutant factor VII has reduced blood coagulation activity relative to wild-type factor VII. These deficiencies are made up for in the teachings of Drake et al and Contrino et al and Dickinson et al and Berkner et al.

Drake et al teach that tissue factor is not expressed on normal vascular endothelial cells (See page 1092, right column). Drake et al teach that tissue factor is expressed on extravascular cells of several normal tissues and in the adventitial layer of the blood vessel wall (see Table 2 and page 1092). Drake et al teach that factor VII and VIIa specifically bind to tissue factor and the resulting biomolecular complex of tissue factor and factor VII or VIIa activates factors IX and X by limited proteolysis, leading ultimately to thrombin generation and fibrin formation (i.e., coagulation) (see page 1087).

Contrino et al teach that tissue factor is expressed on endothelial cells of the tumor vasculature (see entire document).

Dickinson et al teach that lysine-341 of factor VII is important for catalytic or proteolytic function (see page 14380, right column).

Berkner et al teach a form of factor VII, wherein the catalytic active site of factor VII is modified to effectively interrupt the blood coagulation cascade (see entire document). Berkner et al teach that compositions comprising the modified factor VII are useful for treating a variety of conditions involving intravascular coagulation (see column 8, lines 35-67). Berkner et al teach that the serine 344→alanine substitution resulted in decreased coagulant activity of the modified factor VII relative to wild-type factor VII (see column 14).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a composition comprising an immunoconjugate having a mutant factor VII as a targeting domain conjugated to an effector domain, which induces a cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a composition comprising an immunoconjuage having a mutant factor VII as a targeting domain conjugated to an effector domain, which induces a cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Olson et al and Drake et al and Contrino et al and Dickinson et al and Berkner et al because Olson et al teach a ligand-toxin conjugate (i.e., VEGF-toxin) that specifically targets a receptor over-expressed in the endothelial cells of tumor vasculature and almost nondetectable in the vascular endothelium of adjoining normal tissues and Drake et al teach that tissue factor is not expressed

on normal vascular endothelial cells and Contrino et al teach that tissue factor is expressed on endothelial cells of the tumor vasculature. Therefore, it would have been obvious to one skilled in the art to substitute factor VII for VEGF as the targeting domain in the conjugate taught by Olson et al, which would selectively target tissue factor expressed on the endothelial cells of the tumor vasculature in view of Drake et al and Contrino et al. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a composition comprising an immunoconjuage having a mutant factor VII as a targeting domain conjugated to an effector domain, which induces a cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Olson et al and Drake et al and Contrino et al and Dickinson et al and Berkner et al because Drake et al teach that factor VII and VIIa specifically bind to tissue factor and the biomolecular complex of tissue factor and factor VII or VIIa activates factors IX and X by limited proteolysis (i.e., the coagulation cascade) and tissue factor is expressed in various normal tissues and Dickinson et al teach that lysine-341 of factor VII is important for catalytic or proteolytic function and Berkner et al teach that the serine 344→alanine substitution resulted in decreased coagulant activity of the modified factor VII relative to wild-type factor VII. Therefore, it would have been obvious to one skilled in the art to inhibit initiation of the coagulation pathway because Drake et al teach that tissue factor is expressed in various normal tissues and binding of an active administered factor VII-toxin conjugate could induce disseminated intravascular coagulation. Thus, it would have been

obvious to one skilled in the art to produce a composition comprising an immunoconjuage having a mutant factor VII as a targeting domain conjugated to an effector domain, which induces a cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Olson et al and Drake et al and Contrino et al and Dickinson et al and Berkner et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claims 1-3, 6-8, 21-22 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al (U.S. Patent 6,132,729, filed 1/20/1998) in view of Min et al (Cancer Research, 56:2428-2433, 1996) and Contrino et al (Nature Medicine, 2:209-215, 1996) and Dickinson et al (Proc. Natl. Acad. Sci, USA, 93:14379-14384, 1996) and Berkner et al (U.S. Patent 5,861,374, 102(e) date 2/12/96).

The claims have been described supra.

Claims 21-22 further limit parent claim 1 by reciting that the immunoconjugate protein is constructed as a dimer of two identical chains, each having an effector domain and a targeting domain and the effector domain is the Fc region of an IgG1 immunoglobulin.

Thorpe et al teach that factor VII specifically binds to tissue factor and initiates the coagulation cascade (see Figure 1). Thorpe et al teach that tissue

factor is typically not expressed on cells of the blood or the surface of endothelial cells that form the vasculature under normal conditions and expression of tissue factor in the vasculature typically will result in disseminated intravascular coagulation or localized initiation of blood clots or thrombogenesis (see column 17, lines 17-25). Thorpe et al teach that tissue factor is expressed in bronchial mucosa and alveolar epithelial cells in the lung and in glial cells and astrocytes in the nervous system and expression has also been reported in cardiac monocytes, renal glomeruli, and in certain epithelial or mucosal tissues of the intestine, bladder and respiratory tract (see bridging paragraph of columns 16-17). Thorpe et al teach that tissue factor has been connected to the development of the neoplastic phenotype in certain types of tumors and "it has been reasoned that a generalized activation of the coagulation cascade could damage the vasculature leading to access of tumor cells or tumor-cell derived vesicles to the general circulation, allowing such tumor cells to seed and cause metastatic tumor outgrowth." (see column 17, lines 32-42). Thorpe et al teach that a ligand with specificity for the tumor environment may be conjugated to a toxin for specifically targeting molecules expressed on tumor endothelium, but that have little or no expression at the surface of normal endothelial cells (see column 55, lines 23-28 and column 56, lines 26-67). Thorpe et al do not specifically teach that tissue factor is expressed on endothelial cells of the tumor vasculature or an immunoconjugate comprising factor VII or mutant factor VII as a targeting domain conjugated to an IgG1 Fc effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell, wherein

the mutant factor VII has lysine-341→alanine and serine-344→alanine substitutions and has reduced blood coagulation activity relative to wild-type factor VII. These deficiencies are made up for in the teachings of Min et al and Contrino et al and Dickinson et al and Berkner et al.

Min et al teach a ligand-Fc immunoconjugate that inhibits angiogenesis and neovascularization and the immunoconjugate has a prolonged plasma half-life (see page 2430-2433). Min et al teach that the epidermal growth factor-like domain of mouse urokinase was fused (i.e., conjugated) to the hinge, CH2 and CH3 domains of the human IgG1 heavy chain constant region as a disulfide-linked dimer (see page 2430, left column).

Contrino et al have been described supra.

Dickinson et al have been described supra.

Berkner et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a composition comprising an immunoconjuage having a mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a composition comprising an immunoconjugate having a mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic

effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Thorpe et al and Min et al and Contrino et al.and Dickinson et al and Berkner et al because Thorpe et al teach that a ligand with specificity for the tumor environment may be conjugated to a toxin for specifically targeting molecules expressed on tumor endothelium, but that have little or no expression at the surface of various normal endothelial cells and Thorpe et al teach that factor VII specifically binds tissue factor and tissue factor is not expressed on endothelial cells that form the vasculature under normal conditions and Contrino et al teach that tissue factor is expressed on endothelial cells of the tumor vasculature. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a composition comprising an immunoconjugate having a mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Thorpe et al and Min et al and Contrino et al and Dickinson et al and Berkner et al because Min et al teach a ligand-Fc immunoconjugate that inhibits angiogenesis and neovascularization and the immunoconjugate has a prolonged plasma half-life. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a composition comprising an immunoconjuage having a mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell for the treatment of

pathological conditions characterized by neovascularization in view of Thorpe et al and Min et al and Contrino et al and Dickinson et al and Berkner et al because Thorpe et al teach that tissue factor is expressed in various normal tissues and Dickinson et al teach that lysine-341 is important for catalytic or proteolytic function and Berkner et al teach that the serine 344→alanine substitution resulted in decreased coagulant activity of the modified factor VII relative to wild-type factor VII. Therefore, it would have been obvious to one skilled in the art to inhibit initiation of the coagulation pathway because Thorpe et al teach that tissue factor is expressed in normal tissue and binding of an administered active factor VII-Fc immunoconjugate could induce disseminated intravascular coagulation. Thus, it would have been obvious to one skill in the art to produce a composition comprising an immunoconjugate having a mutant factor VII as a targeting domain conjugated to an effector domain, which can induce a cytolytic immune response or cytotoxic effect against a targeted cell for the treatment of pathological conditions characterized by neovascularization in view of Thorpe et al and Min et al and Contrino et al and Dickinson et al and Berkner et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER